

Hepatol Int (2010) 4:386–395
DOI 10.1007/s12072-010-9163-9

REVIEW ARTICLE

Chronic hepatitis B: whom to treat and for how long? Propositions, challenges, and future directions

Sang Hoon Ahn · Henry L. Y. Chan · Pei-Jer Chen · Jun Cheng · Mahesh K. Goenka ·
Jinlin Hou · Seng Gee Lim · Masao Omata · Teerha Piratvisuth · Qing Xie ·
Hyung Joon Yim · Man-Fung Yuen · the APPROACH Working Group

Received: 28 May 2009 / Accepted: 11 December 2009 / Published online: 20 February 2010
© Asian Pacific Association for the Study of the Liver 2010

Abstract Recent guidelines of the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver 2008 update of the “Asian-Pacific consensus statement on the management of chronic

hepatitis B” offer comprehensive recommendations for the general management of chronic hepatitis B (CHB). These recommendations highlight preferred approaches to the prevention, diagnosis, and treatment of CHB. Nonetheless, the results of recent studies have led to an improved

S. H. Ahn
Department of Internal Medicine,
Yonsei University College of Medicine,
250 Sungsan-ro, Seodaemun-gu, Seoul 120-752, South Korea
e-mail: ahnsh@yuhs.ac

H. L. Y. Chan
Department of Medicine and Therapeutics,
9/F, Prince of Wales Hospital,
The Chinese University of Hong Kong, Shatin, N.T.,
Hong Kong, People's Republic of China
e-mail: hlychan@cuhk.edu.hk

P.-J. Chen
Graduate Institute of Clinical Medicine, National Taiwan
University Hospital, 7 Chung-Shan S Road, Taipei, Taiwan
e-mail: peijerchen@ntu.edu.tw

J. Cheng
Institute of Infectious Diseases, Beijing Ditan Hospital,
Capital Medical University, No. 8, Jingshun East Street,
Chaoyang District, 100015 Beijing, People's Republic of China
e-mail: cj@genetherapy.com.cn

M. K. Goenka
Institute of Gastroenterology and Endoscopy,
Apollo Gleneagles Hospitals, 58 Canal Circular Road,
Kolkata 700-054, India
e-mail: dr_mkgoenka@yahoo.co.in

J. Hou
Hepatology Unit, Nanfang Hospital,
Southern Medical University, Guangzhou 510515,
People's Republic of China
e-mail: jlhou@fimmu.com

S. G. Lim
Department of Gastroenterology and Hepatology,
National University Health System,
5 Lower Kent Ridge Road, Singapore 119074, Singapore
e-mail: mdclimg@nus.edu.sg

M. Omata (✉)
Department of Gastroenterology, University of Tokyo,
7-3-1 Hongo Bunkyo-ku, Tokyo 113-0033, Japan
e-mail: momata-ky@umin.ac.jp

T. Piratvisuth
NKC Institute of Gastroenterology and Hepatology,
Songklanagarind Hospital, Prince of Songkla University,
Hat Yai 90110, Thailand
e-mail: teerha.p@psu.ac.th

Q. Xie
Department of Infectious Disease, Ruijin Hospital,
Shanghai Jiaotong University School of Medicine, No.197 Rui
Jin Er Road, 200025 Shanghai, People's Republic of China
e-mail: xieqingrj@yahoo.com.cn

H. J. Yim
Division of Gastroenterology, Department of Internal Medicine,
Korea University Ansan Hospital, 516, Gojan 1-dong,
Danwon-gu, Ansan City, Kyunggi-do 425-707, Korea
e-mail: gudwns21@korea.ac.kr

M.-F. Yuen
Division of Gastroenterology and Hepatology,
The University of Hong Kong, Queen Mary Hospital,
102 Pokfulam Road, Hong Kong, People's Republic of China
e-mail: mfyuen@hkucc.hku.hk

understanding of the disease and a belief that current recommendations on specific therapeutic considerations, including CHB treatment initiation and cessation criteria, particularly in patient populations with special circumstances, can be improved. Twelve experts from the Asia-Pacific region formed the *Asia-Pacific Panel Recommendations for the Optimal Management of Chronic Hepatitis B* (APPROACH) Working Group to review, challenge, and assess relevant new data and inform future updates of CHB treatment guidelines. The significance of and controversy about reported findings were discussed and debated in an expert meeting of the Working Group in Beijing, China, in November 2008. This review paper attempts to identify areas requiring improved CHB management and provide suggestions for future guideline updates, with special emphasis on treatment initiation and duration.

Keywords Chronic hepatitis B (CHB) · Hepatitis B virus (HBV) · Nucleoside/nucleotide analog · Interferon alfa · HBV DNA · ALT

Introduction

Chronic hepatitis B (CHB) is a major global health challenge and a leading cause of liver-related morbidity and mortality within the Asia-Pacific region. To help guide clinicians in their management of patients with CHB, several regional and country expert associations have developed treatment guidelines, incorporating advances in both the understanding of the natural history of the disease and the expanding range of therapeutic options [1–4]. Despite the availability of a large amount of new data on CHB treatment, many issues remain unresolved [1, 5]. In November 2008, 12 experts from the Asia-Pacific region formed the *Asia-Pacific Panel Recommendations for the Optimal Management of Chronic Hepatitis B* (APPROACH) Working Group in an attempt to address issues of “whom to treat and for how long?” The group met at the Beijing Ditan Hospital, China, where relevant data from recent studies were reviewed, assessed, and challenged, with the significance of and controversy about reported findings discussed and debated.

This paper aims to identify the challenges facing current guidelines and discuss propositions for future CHB guideline amendments, with the hope of enhancing antiviral treatment in the region.

Natural history of hepatitis B virus

The hepatitis B virus (HBV) causes chronic infection in 350–400 million people worldwide, 75% of whom are in the Asia-Pacific region, with the majority acquiring the

infection at birth, or within the first 1–2 years of life [6, 7]. HBV is a known human carcinogen [8–10], with research indicating it as a strong risk factor for cirrhosis and hepatocellular carcinoma (HCC) [11, 12].

Three large-scale, long-term, prospective studies looking at cohorts from Hong Kong [13], China [14], and Taiwan [15] assessed the incidence of and risk factors for cirrhosis, HCC, and death from liver disease among CHB patients. Cohorts each included more than 1,000 subjects and were followed for 7–11 years. All three studies came to similar conclusions: HBV DNA concentration is the most important predictor of HCC; the higher the HBV DNA load, the higher the incidence of HCC. These findings, along with data from similar risk prediction studies [16], have led to all major treatment guidelines advocating the elimination of viral replication as the primary aim of CHB treatment [17].

HBV genotype has also been identified to be possibly associated with an increased risk of HCC development [18, 19]. Important differences exist among HBV genotypes and subgenotypes, which display different clinical and virological characteristics [20, 21]. Such differences may affect the natural history and overall progression of the disease, as well as response to treatment.

Genotypes B and C are predominant in Asia, characteristically acquired through vertical transmission in the perinatal period. They are distinct from HBV genotypes A and D, acquired primarily in adulthood and predominant in Western patients [18, 22]. There is increasing evidence that HBV genotype C is associated with more severe liver disease and an increased risk of HCC than HBV genotype B [6, 19].

Despite these prognostic implications, HBV genotype has no substantial impact on the therapeutic response to oral nucleoside or nucleotide analogs [23, 24]. Further studies are needed to understand the implications of HBV genotype, and of particular interest is the need to adopt different treatment initiation and cessation criteria for patients with different genotypes and/or subgenotypes [13]. In addition, studies to address the role of some common HBV variants in the development of HCC, such as pre-S deletions and T1653 mutations, are warranted [25, 26].

Treatment initiation: “whom to treat?”

The decision to commence treatment must balance the likelihood of a sustained treatment response, with the future risk of liver-related morbidity and mortality. Consideration of further factors, including patient age, concurrent illness, medication compliance, liver disease activity, likelihood of long-term benefit, and potential therapeutic risks such as side effects, must be included as

part of a risk–benefit analysis [27]. Cost, drug availability, and the emergence of antiviral resistance are important considerations of particular interest to the Asia-Pacific region.

A large amount of new data have become available in recent years, suggesting that conventional criteria for treatment initiation based on existing disease progression do not necessarily correlate with the future risk of disease complications. There is therefore a need for a fresh appraisal of the current evidence, with subsequent revisions and updates for future guidelines.

Challenges and unresolved issues

Indications for treatment initiation are currently based on three criteria: serum aminotransferase (alanine, ALT; aspartate, AST) levels; serum HBV DNA levels; and histological grade and stage.

Serum ALT level

Current Asian Pacific Association for the Study of the Liver (APASL) recommendations indicate that treatment initiation should be considered in patients with active HBV replication and ALT levels at least twice the upper limit of normal (ULN), but not in patients with persistently normal or minimally elevated ALT levels, except where there is evidence of advanced fibrosis or cirrhosis [1]. Such recommendations are based on the observation that the latter subjects usually experience minimal histological changes and respond poorly in terms of HBeAg seroconversion rate to interferon (IFN) and oral antiviral therapy [1, 12]. Emerging data from several clinical studies indicate that significant liver damage can occur in patients with high viral loads and persistently normal ALT levels, particularly if they are HBeAg negative [28, 29]. These patients are easily excluded from treatment as a result of current ALT-dependent treatment initiation criteria, particularly when liver biopsy is not feasible.

ALT is now thought to be a relatively inaccurate marker of liver fibrosis and may be a better indicator for necroinflammation, correlating poorly with the degree of liver disease, particularly when only single measurements are available. Recent studies suggest that patients with normal serum ALT levels have no or minimal disease progression [30, 31], whereas a substantial proportion of Asian patients with minimally elevated ALT levels have significant histological disease [28]. Another study reported that 23.7% of Asian patients with persistently normal ALT levels had significant histological findings including inflammation and fibrosis [32]. Further studies indicate that a single, high-normal ALT reading (between 0.5 and 1 times the ULN)

indicates a risk of advanced fibrosis in both HBeAg-positive and HBeAg-negative patients [33–35]. In a Hong Kong longitudinal follow-up study, the cumulative risk of disease complications, stratified according to ALT levels on presentation, was found to be highest in patients with ALT levels between one and two times the ULN. Patients with ALT levels between 0.5 and 1 times the ULN also had a significantly increased risk of complications [16], a claim supported by a Korean population study [36].

Another concern of the inaccuracy of ALT as a marker for liver fibrosis is the suitability of an ULN “threshold” due to variability in quoted reference ranges and heterogeneity within target populations. Several variables often not accounted for when determining the “normal” ALT range include age, fasting blood glucose, and serum triglyceride levels, as well as differences in the commercial assays used and the reference populations chosen by each manufacturer to establish its reference range [37]. ALT levels have further been shown to vary according to body mass index (BMI). One study proposed that the current ULN may be set too high, with values close to the abnormal ULN value for someone with a low BMI [38]. Indirect evidence for this comes from cohort studies of healthy patients, which indicated that the ULN should be 30 IU/mL for men and 19 IU/mL for women [37, 39]. Existing regional guidelines do not specify ULN values for serum ALT, but APASL suggests “high normal” (ALT 0.5–1 times ULN) and “low normal” (ALT \leq 0.5 times ULN) to help differentiate ULN values for serum ALT. As ALT ULN varies greatly from laboratory to laboratory, ranging from 36 U/L [40] to 60 U/L [41] in published studies, standardization may not be appropriate. For borderline ALT levels, alternative indicators such as liver biopsy and histology are needed to evaluate the extent of liver damage.

In light of these data, the most recent European Association for the Study of the Liver (EASL) treatment guidelines suggest that abnormal ALT levels together with HBV DNA levels of more than 2,000 IU/mL are sufficient criteria for treatment commencement. A liver biopsy is further recommended for determining the degree of necroinflammation and fibrosis in such patients [3].

Serum HBV DNA level

Quantitation of serum HBV DNA previously utilized an arbitrarily assigned value of 10^5 copies/mL as a criterion for CHB treatment, based on a previous understanding of CHB natural history, and lower sensitivity of previously available viral load quantification assays [42]. HBV DNA levels are currently quantified by polymerase chain reaction (PCR) assays, which can detect HBV DNA levels as low as 100 copies/mL.

In the most recent APASL update, HBV DNA levels in excess of 20,000 IU/mL (or 100,000 copies/mL) and 2,000 IU/mL (or 10,000 copies/mL), together with ALT levels more than two times the ULN, have been proposed as thresholds for treatment of HBeAg-positive and HBeAg-negative hepatitis, respectively. While such HBV DNA thresholds identify the majority of patients with active liver disease, more than 10% of HBeAg-negative CHB patients with persistently or transiently increased serum ALT levels may have serum HBV DNA levels that fall below the recommended cutoff of 2,000 IU/mL [43]. In fact, no single HBV DNA level can confidently differentiate patients with active or inactive liver disease after HBeAg seroconversion [44, 45]. Furthermore, a significant proportion of Asian patients are at continued risk of liver complications despite their HBV DNA levels falling below 10,000 copies/mL [7, 46]. Patients with HBV DNA levels below 2,000 IU/mL are also at a significantly higher risk of developing HCC than uninfected patients [47]. Such studies reinforce the impact of unsuppressed viral load on disease progression and suggest that treatment initiation may need to be considered in patients with lower levels of HBV DNA, especially among patients with advanced fibrosis who have a significant risk of developing HCC [48].

Histological grade

Current guidelines recommend liver biopsy to assess the degree of necroinflammation and liver fibrosis prior to treatment initiation in patients with increased HBV DNA and/or minimally elevated ALT levels (1–2 times the ULN). Liver biopsy is also recommended for patients older than 40 years, especially those with “high normal” ALT levels [1]. Although liver biopsy remains the gold standard for assessing hepatic fibrosis, its use has several limitations including sampling error and intra- or interobserver sampling variability [3, 49, 50]. Inadequate liver biopsy may further pose misleading histological information that precludes cirrhotic patients from antiviral treatment [48]. In addition, although the risk of severe complications is very low (1 in 4,000–10,000), liver biopsy is associated with undesirable procedural risks such as bleeding. Patients potentially opt to avoid such invasive procedures, so there is a need for a simple, reliable, noninvasive alternative, either complementing or eliminating liver biopsy altogether [3, 51].

APPROACH Working Group consensus

Current treatment initiation criteria potentially exclude patients with a high risk of disease progression, particularly patients with increased viral load and normal or minimally elevated ALT levels who are probably not in the

immune-tolerant phase (i.e., >40 years of age). Serum ALT, as one of the key conventional treatment initiation criteria, does not satisfactorily reflect existing liver damage sensitively or specifically and is a weaker risk factor than viral load in predicting future liver disease complications. While the current APASL recommended monitoring approach toward immune-tolerant patients remains suitable, new methods are needed to evaluate liver histology in the setting of normal ALT and high HBV DNA levels. Future CHB treatment initiation recommendations should be based on the primary treatment objective of preventing liver injury, which may be achievable by treating before complications arise, in the majority of patients.

Special populations

Decompensated patients must be treated as soon as possible, as should be patients with persistent disease activity, signified by elevated ALT levels, and abnormal liver function. Decompensated cirrhotic patients with detectable HBV DNA by PCR should also be treated as early as possible [2–4]. Patients with histological evidence of liver damage as indicated by liver biopsy should be treated. Asymptomatic patients with persistently low ALT levels (normal or minimally elevated) and lack of clinical evidence of liver damage (due to refusal of liver biopsy) may also be treated, depending on the likelihood of disease progression after consideration of additional risk factors including age, gender, and family history of HCC.

Use of diagnostic tools

Evaluation of existing liver damage can be established histologically using liver biopsy; however, further research into the applicability of noninvasive tests in various HBV patient populations is of particular interest. Several formulae based on direct and indirect serum markers of hepatic fibrosis focusing on chronic hepatitis C (CHC) have been developed and evaluated [52] but may not be suitable for CHB patients [53, 54]. Noninvasive predictive models developed for CHB patients need further validation by other groups [55–57].

Transient elastography, a diagnostic tool that has recently been introduced as a novel, rapid, noninvasive, and reproducible method to measure liver stiffness, is also of interest. Meta-analyses of studies involving predominantly CHC patients have confirmed a high accuracy of liver stiffness measurements (LSM) in predicting advanced hepatic fibrosis and cirrhosis [58, 59]. The technique has also been validated against histology in several studies including CHB patients [60–62]. Despite the advantages of this technique, its accuracy is inversely related to age and BMI, with LSM failures reported in overweight patients

with a BMI of more than 28 [63, 64]. In addition, major changes in the inflammatory biochemical activity of serum transaminases, induced by liver disease, may affect LSM results [65]. Measurements of liver stiffness are also technically difficult in particular individuals, including patients with ascites and large vessels and patients with a narrow intercostal space [51].

Predictors of disease progression

Future recommendations are needed to promote the adoption of comprehensive assessments for clearly defined common viral replication and liver function parameters, prior to treatment initiation, and at various points during treatment to determine efficacy. Assessments should primarily consist of easily accessible tests including but not limited to HBV DNA level, complete blood counts, prothrombin time, biochemical tests, including AST and ALT, γ -glutamyl transpeptidase, alkaline phosphatase, and serum albumin, and hepatic ultrasonography [1, 3]. Additional testing for further parameters that are not easily accessible, or affordable, such as HBV genotype, and precore and basal core promoter mutations should be supplementary until their role has been properly defined.

Estimation of the risk of disease progression might be possible through the use of a “risk calculator” based on common viral and liver parameters, as demonstrated in other disease areas, including cardiovascular disease and breast cancer [66, 67]. Several independent groups have developed different risk prediction tools based on population or hospital patient natural history cohorts to evaluate the risk of disease progression [11, 13, 15, 16, 18, 68]. These tools include treatment assessment algorithms, within which all potential risk factors, including gender, age, HBeAg status, ALT elevation, cirrhosis status, HBV genotype, and HBV DNA level, are incorporated. Scoring systems translate these factors into risk scores that can be further incorporated into risk function nomograms, offering a means of making a fast, reasonable, and visually explicit estimation of HCC risk [6, 69]. Such a “risk calculator” tool may help identify patients most benefiting from immediate treatment intervention (e.g., a 40-year-old individual with an 80% risk of HCC development in the next 5 years), thereby supporting the objective to treat as early as possible. This tool may also be particularly useful in patients with asymptomatic disease.

A modified treatment paradigm to improve on current patient risk stratification criteria is also important. In addition, further representative studies for the validation of risk calculation models as they evolve are needed and may, in turn, inform the deciding cutoff levels for treatment initiation in specific patient populations. Finally, there is a requirement for future prospective studies to evaluate

antiviral treatment outcomes and likelihood of long-term benefit of therapeutic intervention in specific patient populations, particularly those in the immune-tolerant phase.

Treatment duration: “for how long?”

Treatment duration is dictated by the desired treatment goal, the ideal long-term goal of CHB therapy being the complete suppression of HBV replication, leading to improved quality of life and survival by preventing disease progression, HCC, and death [3, 12, 70]. HBsAg seroclearance, indicating resolution of chronic infection, is the optimal measure of treatment success but is rarely achieved, even with pegylated IFN therapy. Approximately 0.5% of HBsAg carriers will clear HBsAg yearly; most will develop anti-HBs [2]. Similarly, for nucleos(t)ide analogs, only a small proportion of patients can achieve HBsAg seroclearance. Most can achieve only viral suppression, with virological rebound typically occurring upon treatment cessation [71, 72]. Therefore, the issue whether treatment with nucleos(t)ide analogs should be stopped remains controversial.

Challenges and unresolved issues

Three conventional targets of antiviral therapy are addressed within treatment guidelines: sustained undetectable HBV DNA levels by PCR; normalization of ALT levels; and HBeAg seroconversion. More recently, recommendations have incorporated HBsAg seroclearance as an end point for treatment cessation [3].

HBeAg seroconversion and HBeAg-positive patients

Current APASL guidelines state that oral antiviral treatment cessation can be considered in HBeAg-positive patients with HBeAg seroconversion and undetectable HBV DNA levels on two consecutive occasions, with at least 6-month intervals [1]. This is likely based on studies that reported that 66.8 and 85% of spontaneous seroconverters showed sustained remission [35, 41]. Among HBeAg seroconverters, a certain proportion may have a sustained response with relapse rates of 27% reported, shrinking to 11% in patients who had pretreatment HBV DNA levels of 10^8 copies/mL or less [73]. However, HBeAg seroconversion alone does not always signify a sustained treatment response. While it has been suggested that HBeAg positivity is associated with an increased risk of HCC [74], more than 70% of patients with complications of cirrhosis and HCC are HBeAg-negative [16]. Finally, an earlier histological study showed no significant

difference in the incidence of cirrhosis in HBeAg-positive patients when compared with anti-HBe positive patients [75].

Relapse following oral antiviral therapy is also frequent in HBeAg-seroconverted patients. A Taiwanese study on the cumulative development of HBeAg-negative CHB after spontaneous HBeAg seroconversion found that the rate was highest in the first few years following seroconversion, reaching a plateau rate of 25% after approximately 10 years [41]. In a further follow-up study, reactivation of hepatitis following treatment-induced seroconversion was higher (45% of patients) and earlier than that of spontaneous seroconversion (30% of patients) [76]. The majority of Korean patients are infected with HBV genotype C, which is associated with high relapse levels following lamivudine therapy [77]. Relapse rates after HBeAg seroconversion as high as 50% have been reported in these patients [78]. These results suggest that not all patients with HBeAg seroconversion have treatment-free remission after stopping antiviral therapy, especially those among Asian patients.

HBeAg-negative patients

Treatment cessation criteria are less clearly defined for HBeAg-negative patients but include propositions that treatment may be stopped if undetectable HBV DNA levels have been established on three separate occasions, with 6-month intervals [1]. While this is based on studies evaluating treatment duration that suggested that up to 50% of patients have maintained viral suppression following treatment cessation [79–81], the challenge remains in identifying those 50% of patients who would benefit from continued therapy. A study of patients treated with lamivudine for 48 weeks reported similar results, with 73% of patients having HBV DNA levels of <400 copies/mL upon treatment cessation compared with 7% at the end of 24 weeks follow-up. Eight percent of patients who discontinued 48 weeks' adefovir therapy had HBV DNA levels of <1,000 copies/mL after 48 weeks' follow-up compared with 71% of patients who continued therapy through 96 weeks [82, 83]. Consequently, most major guidelines recommend long-term treatment of HBeAg-negative patients or until sustained HBsAg seroclearance has been demonstrated [2, 3].

HBsAg seroclearance

Various studies have shown that patients with spontaneous HBsAg seroclearance have favorable biochemical, virological, and histological parameters, with markedly improved necroinflammation and unchanged or regressed liver fibrosis despite occult HBV infection [84, 85]. HBsAg

seroclearance usually confers favorable outcome if there is no preexisting cirrhosis or viral superinfection, though adverse complications may still occur. Furthermore, HBsAg seroclearance before the age of 50 years is associated with a lower risk of HCC than seroclearance at an older age [86].

Nonetheless, spontaneous or treatment-induced HBsAg seroclearance has long been considered a rare occurrence. Earlier studies reported the spontaneous annual seroclearance rate in high endemic areas to be as low as 0.1 to 0.8% [87]. One recent follow-up study, however, reported the cumulative seroclearance rate in asymptomatic HBeAg-negative patients to be 40% after 25 years. It is worth noting that these patients initially had undetectable HBV DNA and normal ALT levels [87]. The occurrence of HBsAg seroclearance among patients treated with long-term lamivudine is rare [88]. Among HBeAg-negative patients receiving 5 years of adefovir treatment, approximately 5% achieved HBsAg seroclearance [89]. For HBeAg-positive patients receiving 1 year of tenofovir treatment [72] and 2 years of entecavir treatment [71], HBsAg seroclearance occurred in 3 and 5% of patients, respectively. Adopting HBsAg seroclearance as an end point in these cases means potentially committing all patients to long-term treatment. Further studies are needed to define patient groups that have a high chance of HBsAg seroclearance by antiviral treatment.

To complicate the picture further, the reliability of HBsAg seroclearance as an end point has been questioned. One study has shown that 34% of Asian patients who are HBsAg negative have detectable HBV DNA in the liver despite serum levels being undetectable. Another study reported detectable hepatic HBV DNA in 73% of HBsAg-negative Japanese patients, suggesting that most patients continue to harbor HBV infection [90, 91]. The long-term safety of nucleos(t)ide analogs is also an important consideration, with the termination of phase III clevudine trials due to myopathy an indication of the danger in relying on 1-year clinical trial safety profiles [92]. Adefovir and tenofovir can cause nephrotoxicity, and telbivudine is associated with myopathy and neuropathy [93, 94]. There are no serious reports of lamivudine- and entecavir-related toxicity, but further long-term studies are needed [92].

Treatment reinitiation

Defined treatment reinitiation criteria are not mentioned in current CHB management guidelines. Moreover, current re-treatment data are limited. Lamivudine re-treatment studies have involved small patient cohorts (30–60 patients) manifesting high rates of drug resistance due to

lamivudine's low genetic barrier and intermediate potency [95]. Recent studies on entecavir re-treatment appear more promising, as undetectable HBV DNA levels (<300 copies/mL) have been reported in 95% of HBeAg-negative patients 3 years following treatment reinitiation [96].

APPROACH Working Group consensus

Treatment cessation criteria and clinical treatment end points are difficult to define, and the best treatment end point associated with the lowest risk of relapse remains unclear.

The short-term target of antiviral therapy is currently defined in many guidelines as maintained suppression of HBV replication, with or without HBeAg seroconversion [1, 12]. To avoid disease progression and to minimize the risk of resistance, maintained viral suppression is important, particularly in HBeAg-negative and HBeAg-positive patients who have not yet achieved HBeAg seroconversion. For seroconverted patients, recent data have demonstrated that HBeAg seroconversion alone may not signify freedom from risk of disease progression and hepatitis relapse is common after treatment cessation [40, 76, 77]. Current evidence suggests that HBsAg seroclearance would be a preferred end point. In line with recent EASL updates, existing guidelines need to be revised to include sustainable suppression of HBV replication, *with HBsAg seroclearance* as the preferred treatment end point; however, only a small proportion of patients can achieve this end point with currently available oral nucleos(t)ide analogs.

Studies have suggested that serial measurements of HBsAg concentration (titer) may be useful in determining the ideal treatment end point [97], and the quantitation of HBsAg may reflect the amount of covalently, closed, circular DNA inside the hepatocyte [98]. Future studies in this area are of interest.

As the timing of treatment initiation may determine the timing of HBsAg seroclearance [86], and ultimately affect disease progression, the adoption of a preventative approach to CHB treatment, identifying patients at risk using thorough pretreatment evaluation criteria and initiating treatment as early as possible, is strongly advocated.

Patient monitoring should continue to be mandatory upon treatment cessation. While a recent study suggested reinitiation of therapy is effective [96], data remain limited and re-treatment criteria should be the same as those for treatment initiation, as indicated in current APASL or American Association for the Study of Liver Diseases guidelines.

Finally, sustained HBeAg seroconversion may remain an appropriate treatment goal for some patients, for example, young HBeAg-positive patients without advanced disease.

As indicated in current guidelines, 6–12 months of consolidation therapy and monitoring for relapse are crucial upon treatment cessation in these patients [1–3]. Determining the risk of disease progression and HCC development in these patients through employment of a “risk calculator” may help answer the crucial questions of “whom to treat” and “for how long”?

Summary

Current challenges and considerations for future guidelines amendments on “whom to treat” (Table 1) and “for how long” (Table 2) are summarized below.

Table 1 Treatment initiation: whom to treat?

<i>Current challenges</i>
Current, stringent treatment initiation criteria may exclude HBV-infected patients at high risk of HCC from treatment
Routine invasive liver biopsy poses clinical limitations, with variable validity as well as potential patient compliance issues; alternative noninvasive means of assessing liver fibrosis are required
<i>APPROACH consensus</i>
Symptomatic patients must be treated as early as possible
For asymptomatic patients refusing liver biopsy, noninvasive fibrosis assessment should be considered and appropriate risk prediction/calculation completed
Noninvasive fibrosis assessments should be further studied for routine use, instead of liver biopsy, before decisions are made to initiate or cease treatment
An improved treatment assessment algorithm or risk calculator, incorporating all HCC risk factors and common liver parameters, is required to aid hepatologists in redefining treatment initiation criteria

Table 2 Treatment cessation: for how long?

<i>Current challenges</i>
Existing treatment end points have not been demonstrated to sufficiently prevent reactivation or disease progression
Achieving treatment goals and defining appropriate clinical treatment end points are often difficult
Treatment end points are constantly evolving as the understanding of CHB natural history and factors associated with disease progression improves
<i>APPROACH consensus</i>
HBsAg seroclearance is currently the single preferred treatment end point for inclusion in future recommendations and more research is required to determine its likelihood in specific patient populations
HBeAg seroconversion may continue to be an appropriate end point accompanied by undetectable HBV DNA for certain patients with a low, predetermined risk of HCC development
The duration of consolidated treatment after HBeAg seroconversion requires further study with newer antiviral agents, and routine patient monitoring for relapse should remain mandatory upon treatment cessation in all CHB patients

Acknowledgments Bristol-Myers Squibb provided an unrestricted educational grant to accredited medical education provider, Adrenalin Strategies (Australia), for management of the APPROACH Working Group meeting. Editorial support for the development of this report was provided by Adrenalin Strategies (Australia) and MediTech Media (Singapore).

Conflict of interest statement Sang Hoon Ahn has received research support from Bristol-Myers Squibb and has acted as an advisor and lecturer for Bristol-Myers Squibb, GlaxoSmithKline, and Novartis Pharmaceuticals.

Henry L. Y. Chan has served on the Advisory Board of Bristol-Myers Squibb, Novartis Pharmaceuticals, Pharmasset, and Schering Plough Pharmaceuticals.

Jinlin Hou has served on the Advisory Board of Bristol-Myers Squibb and Novartis Pharmaceuticals and is on the speaker's bureau for GlaxoSmithKline, Novartis Pharmaceuticals, and Bristol-Myers Pharmaceuticals.

Seng Gee Lim has served on the Advisory Board of Bristol-Myers Squibb, Novartis Pharmaceuticals, and Schering Plough Pharmaceuticals and is on the speaker's bureau for GlaxoSmithKline, Novartis Pharmaceuticals, and Bristol-Myers Pharmaceuticals.

Masao Omata has served on the Advisory Board of Bristol-Myers Squibb, Pfizer, and Roche and is on the consulting board for Boehringer Ingelheim, Merck, and Taiho Pharmaceutical.

Teerha Piratvisuth has served on the Advisory Board of Novartis Pharmaceuticals, Roche, GlaxoSmithKline, and Schering Plough Pharmaceuticals.

Man-Fung Yuen has served on the Advisory Board of Bristol-Myers Squibb and GlaxoSmithKline and is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Pharmaceuticals, and Roche Diagnostics.

References

- Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008;2:263–283
- Lok ASF, McMahon BJ. AASLD practice guidelines. Chronic hepatitis B. *Hepatology* 2007;45:507–539
- European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol* 2009;50:227–242
- Keeffe EB, Dieterich DT, Han SHB, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol* 2008;6:1315–1341
- Tong MJ, Hsien C, Hsu L, Sun HE, Blatt LM. Treatment recommendations for chronic hepatitis B: an evaluation of current guidelines based on a natural history in the United States. *Hepatology* 2008;48:1070–1078
- Yuen MF, Tanaka Y, Fong DYT, Fung J, Wong DKH, Yuen JCH, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009;50:80–88
- Lai CL, Yuen MF. The natural history of chronic hepatitis B and its treatment: a critical evaluation of standard treatment criteria and end points. *Ann Intern Med* 2007;147:58–61
- International Agency for Research on Cancer. Hepatitis viruses. In: IARC monographs on the evaluation of carcinogenic risks to humans. Vol 59. Lyon (France): WHO Press; 1995. 8
- Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. In: IARC CancerBase No. 5 Version 2.0 (ed). Lyon (France): IARC Press; 2004
- World Health Organization. Global burden of cancer. In: Cancer. Geneva; 2009
- Han KH, Ahn SH. How to predict HCC development in patients with chronic B viral liver disease? *Intervirology* 2005;48:23–28
- Zoulim F, Perrillo R. Hepatitis B: reflections on the current approach to antiviral therapy. *J Hepatol* 2008;48 Suppl 1 :S2–S19
- Chan HL, Tse CH, Mo F, Koh J, Wong VWS, Wong GLH, et al. High viral load and hepatitis B virus subgenotype C are associated with an increased risk of hepatocellular carcinoma. *J Clin Oncol* 2008;26:177–182
- Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006;101:1797–1803
- Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65–73
- Yuen MF, Yuan HJ, Wong DKH, Chan AOO, Wong BCY, Lai KC, et al. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005;54:1610–1614
- Sherman M. Predicting survival in hepatitis B. *Gut* 2005;54:1521–1523
- Yuen MF, Tanaka Y, Shinkai N, Poon RT, But DYK, Fong DYT, et al. Risk for hepatocellular carcinoma with respect to hepatitis B virus genotypes B/C, specific mutations of enhancer II/core promoter/precore regions and HBV DNA levels. *Gut* 2008;57:98–102
- Chan HL, Hui AY, Wong ML, Tse AML, Hung LCT, Wong VWS, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. *Gut* 2004;53:1494–1498
- Yang HI, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. *J Natl Cancer Inst* 2008;100:1134–1143
- Chan HL, Tsui SK, Tse CH, Ng EYT, Au TCC, Yuen L, et al. Epidemiological and virological characteristics of two subgroups of genotype C hepatitis C virus. *J Infect Dis* 2005;191:2022–2032
- Kao JH. Role of viral factors in the natural course and therapy of chronic hepatitis B. *Hepatol Int* 2007;1:415–430
- Yuen MF, Wong DK, Sablon E, Yuan HJ, Sum SM, Hui CK. Hepatitis B virus genotypes B and C do not affect the antiviral response to lamivudine. *Antivir Ther* 2003;8:531–534
- Chan HL, Wong ML, Hui AY, Chim AM, Tse AM, Hung LC. Hepatitis B virus genotype has no impact on hepatitis B e antigen seroconversion after lamivudine treatment. *World J Gastroenterol* 2003;9:2695–2697
- Fang ZL, Sabin CA, Dong BQ, Wei SC, Chen QY, Fang KX, et al. Hepatitis B virus pre-S deletion mutations are a risk factor for hepatocellular carcinoma: a matched nested case-control study. *J Gen Virol* 2008;89:2882–2890
- Tanaka Y, Mukaide M, Orito E, Yuen MF, Ito K, Kurbanov F, et al. Specific mutations in enhancer II/core promoter of hepatitis B virus subgenotypes C1/C2 increase the risk of hepatocellular carcinoma. *J Hepatol* 2006;45:646–653
- Osborn MK, Lok ASF. Antiviral options for the treatment of chronic hepatitis B. *J Antimicrob Chemother* 2006;57:1030–1034
- Tsang PSY, Trinh H, Garcia RT, Phan JT, Nghiem BHA, Nguyen H, et al. Significant prevalence of histologic disease in patients with chronic hepatitis B and mildly elevated serum alanine aminotransferase levels. *Clin Gastroenterol Hepatol* 2008;6:569–5674

29. Park JY, Park YN, Kim DY, Paik YH, Lee KS, Moon BS, et al. High prevalence of significant histology in asymptomatic chronic hepatitis B patients with genotype C and high serum HBV DNA levels. *J Viral Hepat* 2008;15:615–621
30. Park BK, Park YN, Ahn SH, Lee KS, Chon CY, Moon YM, et al. Long-term outcome of chronic hepatitis B based on histological grade and stage. *J Gastroenterol Hepatol* 2007;22:383–388
31. Tai DI, Lin SM, Sheen IS, Chu CM, Lin DY, Liaw YF. Long-term outcome of hepatitis B e antigen-negative hepatitis B surface antigen carriers in relation to changes of alanine aminotransferase levels over time. *Hepatology* 2009;49:1859–1867
32. Gui H, Xie Q, Wang H, Lin Z, Cai W, Zhou X, et al. Predictors of significant histological findings in chronic hepatitis B patients with persistently normal ALT levels. In: Proceedings of the American Association for the Study of Liver Disease (AASLD); 2007; Boston, MA. *Hepatology* 2007;46 Suppl 1:653A
33. Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, et al. Evaluation of alanine transaminase and hepatitis B virus DNA to predict liver cirrhosis in hepatitis B e antigen-negative chronic hepatitis B using transient elastography. *Am J Gastroenterol* 2008;103:3071–3081
34. Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, et al. Clinical factors associated with liver stiffness in hepatitis B e antigen-positive chronic hepatitis B. *Clin Gastroenterol Hepatol* 2009;7:227–233
35. Fung J, Lai CL, But D, Wong D, Cheung TK, Yuen MF. Prevalence of fibrosis and cirrhosis in chronic hepatitis B: implications for treatment and management. *Am J Gastroenterol* 2008;103:1421–1426
36. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. *BMJ* 2004;328:983
37. Kariv R, Leshno M, Beth-Or A, Strul H, Blendis L, Kokia E, et al. Re-evaluation of serum alanine aminotransferase upper normal limit and its modulating factors in a large-scale population study. *Liver Int* 2006;26:445–450
38. Piton A, Poynard T, Imbert-Bismut F, Khalil L, Delattre J, Pelissier E, et al. Factors associated with serum alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. MULTIVIRC Group. *Hepatology* 1998;27:1213–1219
39. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002;137:1–10
40. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002;35:1522–1527
41. Lai M, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. *J Hepatol* 2007;47:760–767
42. Lok ASF, McMahon BJ. AASLD practice guidelines. Chronic hepatitis B. *Hepatology* 2001;34:1225–1241
43. Papatheodoridis G, Manesis E, Manolakopoulos S, Goulis J, Chrysanthos N, Bilalis A. HBeAg-negative chronic hepatitis B (CHBe-) in chronic HBV patients with serum HBV-DNA levels below 2000 IU/mL. In: Proceedings of the European Association for the Study of the Liver (EASL); 2007; Barcelona, Spain. *J Hepatol* 2007;46: Suppl 1:S183
44. Chan HL, Wong ML, Hui AY, Hung LC, Chan FK, Sung JJ. Use of hepatitis B virus DNA quantitation to predict hepatitis B e antigen reversion in cases of chronic hepatitis B. *J Clin Microbiol* 2003;41:4793–4795
45. Chu CJ, Hussain M, Lok ASF. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. *Hepatology* 2002;36:1408–1415
46. Yuan HJ, Yuen MF, Wong DKH, Sablon E, Lai CL. The relationship between HBV-DNA levels and cirrhosis-related complications in Chinese with chronic hepatitis B. *J Viral Hepat* 2005;12:373–379
47. Iloeje UH, Yang HI, Su J. HBV viral load less than 104 copies/mL is associated with significant risk of hepatocellular carcinoma in chronic hepatitis B patients: an update from the R.E.V.E.A.L. HBV study. In: Proceedings of the American Association for the Study of Liver Disease (AASLD); 2007; Boston, MA. *Hepatology* 2007;46 Suppl 1:640A
48. Chan HL. Revisiting the treatment recommendations for chronic hepatitis B. *Hepatology* 2009;49:700
49. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003;38:1449–1457
50. Omata M. Regression of liver fibrosis in patients treated by interferon. *Intern Med* 2004;43:887–888
51. Han KH, Yoon KT. New diagnostic methods for liver fibrosis and cirrhosis. *Intervirology* 2008;51 Suppl 1:11–16
52. Pinzani M, Vizzutti F, Arena U, Marra F. Technology insight: noninvasive assessment of liver fibrosis by biochemical scores and elastography. *Nat Clin Pract Gastroenterol Hepatol* 2008;5:95–106
53. Wai CT, Cheng CL, Wee A, Dan YY, Chan E, Chua W, et al. Non-invasive models for predicting histology in patients with chronic hepatitis B. *Liver Int* 2006;26:666–672
54. Chang PE, Lui HF, Chau YP, Lim KH, Yap WM, Tan CK, et al. Prospective evaluation of transient elastography for the diagnosis of hepatic fibrosis in Asians: comparison with liver biopsy and aspartate transaminase platelet ratio index. *Aliment Pharmacol Ther* 2008;28:51–61
55. Hui AY, Chan HL, Wong VW, Liew CT, Chim AM, Chan FK, et al. Identification of chronic hepatitis B patients without significant liver fibrosis by a simple noninvasive predictive model. *Am J Gastroenterol* 2005;100:616–623
56. Kim HS, Kim JK, Park YN, Myung SM, Pang MS, Yoon KT, et al. Non-invasive assessment of liver fibrosis by measuring the liver stiffness and biochemical markers in chronic hepatitis B patients. *Korean J Med* 2007;72:459–469
57. Kim SU, Ahn SH, Park JY, Kang W, Kim DY, Park YN, et al. Liver stiffness measurement in combination with noninvasive markers for the improved diagnosis of B-viral liver cirrhosis. *J Clin Gastroenterol* 2009;43:267–271
58. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology* 2008;134:960–974
59. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systemic review and meta-analysis. *Clin Gastroenterol Hepatol* 2007;5:1214–1220
60. Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, de Lédinghen V, et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. *Liver Int* 2009;29:242–247
61. Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (FibroScan) for liver fibrosis in chronic hepatitis B. *J Viral Hepat* 2009;16:36–44
62. Kim DY, Kim SU, Ahn SH, Park JY, Lee JM, Park YN, et al. Usefulness of FibroScan for detection of early compensated liver cirrhosis in chronic hepatitis B. *Dig Dis Sci* 2008;54:1758–1763
63. Kettaneh A, Marcellin P, Douvin C, Poupon R, Ziol M, Beaugrand M, et al. Features associated with success rate and performance of FibroScan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. *J Hepatol* 2007;46:628–634

64. Foucher J, Castéra L, Bernard PH, Adhoute X, Laharie D, Bertet J, et al. Prevalence and factors associated with failure of liver stiffness measurement using FibroScan in a prospective study of 2114 examinations. *Eur J Gastroenterol Hepatol* 2006;18:411–12
65. Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. *J Viral Hepat* 2007;14:360–369
66. Domchek SM, Eisen A, Calzone C, Stopfer J, Blackwood A, Weber BL. Application of breast cancer risk prediction models in clinical practice. *J Clin Oncol* 2003;21:593–601
67. L'Italien G, Ford I, Norrie J, LaPuerta P, Ehreth J, Jackson J, et al. The cardiovascular event reduction tool (CERT): a simplified cardiac risk prediction model developed from the West of Scotland Coronary Primary Prevention Study (WOSCOPS). *Am J Cardiol* 2000;85:720–724
68. Chen CJ, Iloeje UH, Yang HI. Long-term outcomes in hepatitis B: the REVEAL-HBV study. *Clin Liver Dis* 2007;11:797–816
69. Chen CJ, Yang HI, Iloeje UH, Jen CL, You SL, Sherman M, et al. HBV DNA & genotype predict HCC. In: Levin J, editor. *Digestive Disease Week 2007*. Washington (DC); 2007
70. Fung J, Lai CL, Yuen MF. New paradigms for the treatment of chronic hepatitis B. *J Gastroenterol Hepatol* 2008;23:1182–1192
71. Gish RG, Lok ASF, Chang TT, de Man RA, Gadano A, Sollano J, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology* 2007;133:1437–1444
72. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008;359:2442–2455
73. Yeh CT, Hsu CW, Chen YC, Liaw YF. Withdrawal of lamivudine in HBeAg-positive chronic hepatitis B patients after achieving effective maintained virological suppression. *J Clin Virol* 2009;45:114–1148
74. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002;347:168–174
75. Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Hepatology* 1988;8:493–496
76. Lim SG, Oo AM, Wasser S. Treatment-induced HBeAg seroconversion is a poor therapeutic endpoint. In: *Proceedings of the American Association for the Study of Liver Disease (AASLD)*; 2007; Boston, MA. *Hepatology* 2007;46 Suppl 1:653A
77. Chien RN, Yeh CT, Tsai SL, Chu CM, Liaw YF. Determinants for sustained HBeAg response to lamivudine therapy. *Hepatology* 2003;38:1267–1273
78. Song BC, Suh DJ, Lee HC, Chung YH, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. *Hepatology* 2000;32:803–806
79. Fung SK, Wong F, Hussain M, Lok ASF. Sustained response after a 2-year course of lamivudine treatment of hepatitis B e antigen-negative chronic hepatitis B. *J Viral Hepat* 2004;11:432–438
80. Chan HL, Wang H, Niu J, Chim AM, Sung JJ. Two-year lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B: a double-blind, placebo-controlled trial. *Antivir Ther* 2007;12:345–353
81. Chien RN, Liaw YF. Short-term lamivudine therapy in HBeAg-negative chronic active hepatitis B in Taiwan. *Antivir Ther* 2006;11:947–952
82. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005;352:2673–2681
83. Marcellin P, Lau GKK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004;351:1206–1217
84. Yuen MF, Wong DKH, Sablon E, Tse E, Ng IOL, Yuan HJ, et al. HBsAg seroclearance in chronic hepatitis B in the Chinese: virological, histological, and clinical aspects. *Hepatology* 2004;39:1694–1701
85. Ahn SH, Park YN, Park JY, Chang HY, Lee JM, Shin JE, et al. Long-term clinical and histological outcomes in patients with spontaneous hepatitis B surface antigen seroclearance. *J Hepatol* 2005;42:188–194
86. Yuen MF, Wong DKH, Fung J, Ip P, But D, Hung I, et al. HBsAg seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. *Gastroenterology* 2008;135:1192–1129
87. Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. *Hepatology* 2007;45:1187–1192
88. Chang TT, Lai CL, Chien RN, Guan R, Lim SG, Lee CM, et al. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2004;19:1276–1282
89. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1741–1743
90. Kim YS, Jang JY, Eun SH, Cheon YK, Kim YS, Moon JH, et al. Detection of intrahepatic HBV DNA in HBsAg-negative liver diseases. *Korean J Hepatol* 2006;12:201–208
91. Momosaki S, Nakashima Y, Kojiro M, Tabor E. HBsAg-negative hepatitis B virus infections in hepatitis C virus-associated hepatocellular carcinoma. *J Viral Hepat* 2005;12:325–329
92. Fleischer RD, Lok ASF. Myopathy and neuropathy associated with nucleos(t)ide analog therapy for hepatitis B. *J Hepatol* 2009;51:787–791
93. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009;136:486–495
94. Marcellin P, Chang T, Lim SG, Tong MJ, Sievert W, Shiffman ML, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive hepatitis B. *N Engl J Med* 2003;348:808–816
95. Shin JW, Park NH, Park JH, Park JH, Jeong ID, Bang SJ, et al. Efficacy of lamivudine re-treatment for relapsed patients after an initial lamivudine therapy in HBeAg-positive chronic hepatitis B. *J Viral Hepat* 2005;12:393–397
96. Shouval D, Lai CL, Chang TT, Tan CK. Three years of entecavir (ETV) re-treatment of HBeAg(-) ETV patients who previously discontinued ETV treatment: results from study ETV-901. In: *Proceedings of the American Association for the Study of Liver Diseases (AASLD)*; 2008; San Francisco, CA. *Hepatology* 2008;48 Suppl 1:722A
97. Gish RG, Lau DT, Schmid P, Perrillo R. A pilot study of extended duration peginterferon alfa-2a for patients with hepatitis B e antigen-negative chronic hepatitis B. *Am J Gastroenterol* 2007;102:2718–2723
98. Chan HL, Wong VW, Tse AM, Tse CH, Chim AM, Chan HY, et al. Serum hepatitis B surface antigen quantitation can reflect hepatitis B virus in the liver and predict treatment response. *Clin Gastroenterol Hepatol* 2007;5:1462–1468